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(54) Title: FAST DISINTEGRATING ORAL DOSAGE FORMS

(57) Abstract: The present invention relates to the method of preparation of fast disintegrating oral dosage forms, such as tablets, which disintegrates rapidly in the mouth within 15 seconds without the need of water. The method of this invention is particularly suitable for the actives with low bulk density, poorly compressible and moisture sensitive actives.

FAST DISINTEGRATING ORAL DOSAGE FORMS

Field of the invention

The present invention relates to the method of preparing solid dosage form by dry granulation technique for oral administration which disintegrates/dissolves rapidly in mouth.

Background of the invention

Oral route is the most preferred route for the administration of a wide variety of drugs to produce systemic effects. Of drugs that are administered orally, solid oral dosage forms represent the preferred class of product. As tablet represents an unit dosage form in which one usual dose of the drug has been accurately placed, it avoids errors in the total dose to be taken when the drug is self administered by the patient. The current and projected growth of the elderly population in the world is well recognized and 20 % of the world population is 60 years of age or older who receives about 50 % of the medicines prescribed. But oral dosage forms such as tablets/capsules need to be swallowed by patient. In the case of geriatric patients, difficulty in swallowing the oral dosage form (especially conventional tablets or capsules) is observed. Similar is the case with pediatric patients. Oral administration of the drugs is difficult in patients having concomitant vomiting or diarrhoea. These factors led to the invention in the field of delivering the drug in an easy to ingest way, to overcome such problems. For those patients who face difficulty in swallowing the whole dosage form, physicians recommend delivery of drugs in suitable dosage forms such as solutions, suspensions, emulsions, sublingual tablets, buccal tablets, chewable tablets or fast disintegrating tablets, which does not involve swallowing of whole tablet or capsules. Fast dissolving or fast disintegrating dosage form is one of the advantageous methods to deliver the drugs to such patients.

"Fast dissolvable or disintegrable" means that the rapidly water soluble ingredients will dissolve sufficiently to allow ingestion as a non gritty solution or slurry in less than 90 seconds. Fast dissolvable or fast disintegrating dosage forms are meant to disintegrate immediately upon contact with the saliva leading to faster release of the drugs in the oral cavity. Patients who are reluctant to swallow the dosage form or the patient with severe vomiting or diarrhoea can be treated easily. By administering the fast disintegrating dosage forms, faster absorption of the drug occurs through buccal mucosa and it may reduce the first pass metabolism leading to better efficacy of the drug.

Fast disintegrating dosage forms are advantageous to deliver drugs even for local application of the drug in the oral cavity. This dosage form enhances the clinical effects (efficacy) of some drugs through pregastric absorption from mouth, pharynx, and esophagus

leading to an increase in bioavailability and a reduction in side effects because of avoidance of first-pass liver metabolism.

Different techniques are available for the preparation of fast disintegrating dosage forms. These techniques are:

- spray drying
- freeze drying
- direct compression
- dry granulation
- wet granulation.

All the methods mentioned above have their own limitations for the preparation of the fast disintegrating dosage forms. Spray drying technique involves spraying the drug and/or other excipients blend into a chamber maintained at a higher temperature. As a result, this technique is not suitable for application to thermolabile drugs. Spray drying technology also leads to a very poor out put and is found to be very expensive.

Feasibility of manufacturing fast dissolving dosage form in a large scale using freeze drying technique has not been found to be so effective. It is time consuming and the scale up of the technique is quite difficult. The Zydis tablets, for example, prepared by this technique are so fragile that the matrix material must be formed by freeze-drying in an individual tablet sized-container. Tablets manufactured by this technology require special type of packaging. Such tablets need to be carefully handled during dispensing and actual administration to the patients, since they are prone to breakage. Moreover, freeze-drying is not possible for highly water-soluble drugs and for a drug having a dose of more than 500 mg.

In wet granulation technique, core becomes very hard so it is difficult to obtain fast dissolving / fast disintegrating tablets. Wet granulation leads to coarse dispersion in the oral cavity giving poor patient compliance. Use of solvents and additional drying step makes this technique expensive.

Direct compression, using directly compressible excipients is the most commonly used method of preparing fast disintegrating tablets. Directly compressible excipients are very coarse and granular in nature and give a coarse dispersion in the mouth with decreased mouth feel and compliance. It is very difficult to prepare fast disintegrating tablets with drugs having very low bulk density, higher dose and poor flow property using this technique.

US 6,099,863 (Janssen Pharmaceutica) describes a fast-dissolving galanthamine hydrobromide tablet prepared using spray dried carrier as a diluent which is a mixture of

lactose monohydrate and micro crystalline cellulose (75:25), and a disintegrant through a direct compression process for preparing tablets.

US 5,298,261 (Oregon Freeze Dry Inc.) describes a vacuum drying process to prepare rapidly disintegrating tablets. Vacuum drying a frozen mixture containing a gum, carbohydrates and a solvent in a tablet shaped mold produced tablets with enhanced structural integrity compared with that of traditional molded tablets. However, there is always a risk of residual solvents in the tablets prepared by this method.

EP 1120109 (Pfizer Prod. Inc.) describes a non-friable, rapidly disintegrating, fast-dissolving dosage forms produced from pharmaceutically acceptable steam extruded polymers. Solid dosage form dissolves in the mouth and is particularly useful for subjects who require or desire oral medication but have difficulty in swallowing standard oral dosage forms such as tablets or subjects suffering from emesis. Solid dosage forms are also useful for rapid drug delivery as vaginal or rectal suppositories or oral delivery of veterinary drugs.

US 6,010,719 (Universiteit Gent) describes a freeze dried disintegrating tablets, containing one therapeutic agent, a matrix forming agent selected from the group of maltodextrins having a dextrose equivalent value in between 12 and 40, isomalt and mixtures thereof, the weight ratio between said matrix forming agent and binding agent being comprised between 2:1 and 50:1.

US Pat. No. 6,083,531 (Novartis Consumer Health SA) describes an improved technique for preparing a rapidly dispersing tablet by preparing a suspension or solution of the active ingredient by dispersing or dissolving it in a solvent together with all other components of the compositions and dispensing into molds e.g. blisters and then drying either by simple storage at room temperature or at elevated temperature or by microwave radiation either at normal pressure or at reduced pressure. However, the risk of residual solvent in the final dosage form can not be ruled out.

US 4,866,046 (Top Laboratories) describes an aspirin tablet that rapidly dissolves in the oral, preferably sublingual, cavity within 2-60 seconds. This tablet provides rapid absorption of aspirin from the saliva into the blood stream. The sublingual tablet is prepared by compressing into slugs a mixture of starch (10 % moisture), acetylsalicylic acid, flavor and sweetener. The slugs are then ground (14-16 # size) and recompressed into tablets. An amino acid may also be used with aspirin for solubilizing and as a taste neutralizing agent.

WO 9414422 (Oregon Freeze Dry) describes the formulation of a rapidly disintegrating tablet including a partially collapsed matrix network that has been vacuum dried above the collapse temperature of the matrix.

WO 9501782 (Scherer Corporation) describes an improved technique for preparing a rapidly dispersing tablet by adding xanthan gum to a liquid admixture of solvent, carrier components and a granular agent. The xanthan gum facilitates suspension of the therapeutic agent in the liquid admixture, without affecting the dispersion quality and texture of the tablet in the patient's mouth.

None of the fast-disintegrating/mouth disintegrating/rapidly disintegrating tablets has been prepared by means of dry granulation technology which has the following advantages over other techniques of preparation:

a) it can be used for all types of drugs including moisture sensitive and heat sensitive.
b) it can be used for drugs having very low bulk density
c) it can be used for poorly compressible drugs and drugs having poor flow property.
d) the tablets of the present invention can be packed into regular bottles, blister, strip pack or sachets.
e) the tablets can be stored in bulk in drums to be packaged subsequently. Moreover conventional tablet packaging feeders can be used for packing purpose.
f) the process of dry granulation is cost effective as it avoids solvents, and the processes of drying like freeze drying, spray drying etc.
g) this reduces overall reduction in capital expenditure (conventional processing, packaging, and storage facilities)

Objects of the present invention

The main object of the present invention is to prepare fast disintegrating dosages forms for oral administration by dry granulation technique. The dosage forms prepared according to the present invention may be in the form of tablets, wafers, granules, or granules packed as such along with other pharmaceutically acceptable additives in a suitable package which upon contact with water, saliva or aqueous solution disintegrates within a few seconds.

Another object of the invention is to provide a process for preparing rapidly disintegrating dosage form by roller compaction or slugging of the active ingredient in combination with other excipients.

A further object of the invention is to provide a process for preparing rapidly disintegrating dosage form suitable for moisture sensitive drugs such as aspirin.

A still further object of the invention is to provide a process for preparing rapidly disintegrating dosage form suitable for drugs having low bulk density such as celecoxib.

A further object of the invention is to provide a fast disintegrating dosage form with increased bioavailability.

Still another object of the invention is to provide fast disintegrating dosage form which may have faster absorption.

Yet another object of the invention is to obtain rapidly disintegrating / fast dissolving tablets of various classes of drugs prepared by dry granulation technique of the present invention for the treatment and prophylactic use in humans.

Summary of invention

The present invention provides a process for preparing solid dosage form or a pharmaceutical composition for oral administration by dry granulation process which disintegrates/dissolves rapidly in mouth. The said dosage form may be in the form of tablets, wafers, granules, or granules packed as such along with other pharmaceutically acceptable additives in a suitable package which upon contact with water, saliva or aqueous medium disintegrates within a few seconds.

In the present invention, superior fast dissolving or fast disintegrating dosage form has been prepared by means of dry granulation. The process of the present invention involves three steps. In the first step, the high-density flakes or slugs of either the mixture of active pharmaceutical ingredient (API) and pharmaceutically acceptable excipients or API alone or excipients alone may be obtained by means of roller compaction or slugging. In second step, the obtained flakes or slugs are screened using suitable equipment such as oscillating granulator, to obtain granules of desired size. In third step, these granules are compressed into tablets, or processed suitably to obtain wafers or may be packed as such in suitable packaging.

Detailed description of the invention

Present invention relates to the process of preparing solid oral dosage form which disintegrates rapidly upon contact with water, saliva or other aqueous medium by dry granulation technique and pharmaceutical composition prepared according to said procedure. The dosage form prepared according to the process of the present invention generally disintegrates in the mouth within 5- 90 seconds.

The present invention provides a pharmaceutical composition prepared according to the process of the present invention, consisting of compacted mass i.e. granulates, comprising of at least one active pharmaceutical agent, along with superdisintegrant and other necessary pharmaceutical excipients. This compacted mass is milled and sieved to obtain granules, which is then compressed into tablets, wafers- packed as such in suitable packaging.

The granules are obtained by sieving of compacted flakes, which do not possess uniform shape and discrete boundaries and may be divided into smaller granules. The

invention specifically relates to preparation/compaction of the granules that are in size ranging from 25 to 300 μm and preferably 50 to 200 μm into tablets.

The tablets manufactured using the said granules may have hardness between 2 to 15 Kp, a friability of less than 1% when measured by U.S.P. apparatus. The said tablet may be manufactured using conventional/traditional tabletting machine and may be packaged using conventional packaging machine.

One of the principle advantages of the fast disintegrating tablets of the present invention is that they can be manufactured and stored in drums, bulk bins or hoppers, after tablet compression as is typical for tablets in the pharmaceutical industry. This is a property which is not found in most of the rapidly disintegrating tablets because of their friability. In turn, this attribute provides several significant advantages. With most friable, orally disintegrating tablets, the limiting step in production is the speed at which the tablets can be individually handled and placed in a protective, usually specially designed, blister-style package. The tablets are too fragile to withstand the forces involved in being dumped into the bulk- hopper of a packager or into some other form of intermediate or long-term storage vessel. Thus, the speed of production of the tablets is limited by the rate of packaging.

In accordance with the present invention, however, because of the relatively low friability and the hardness of the resulting orally dissolvable tablets, they can be dumped into a hopper in bulk or can be stored in drums or other containers. This allows the manufacturer to complete the production of the tablets at a maximum tabletting speed. Tablet presses can then be dedicated to other products while the orally disintegrable tablets of the present invention are packaged as is convenient.

Storing in bulk, in accordance with the invention, does not mean that tablets need to be stored for a long time. The residence time of tablets as they are dumped, in bulk, into the feed hopper of a high speed packager is contemplated.

The present invention allows for better quality control of tablets before they are packaged. This is of tremendous significance to the cost of production. Standard quality control procedures on orally disintegrable tablets involves testing the tablets that results from the line, i.e. tablets that have already been packaged. If a lot or batch of tablets has failed, the materials and the packaging may be lost. In some instances, the cost of the packaging is significantly higher than the cost of the drug itself. By unshackling the tablet production and tablet packaging operations, one can test the tablet before packing, thereby eliminating the added expense of throwing away perfectly good packaging.

In addition, because of the relatively low friability and hardness of the orally dissolvable tablets prepared according to the present invention, it is possible to provide tablets in a cheaper and a cost effective packaging. Currently, fragile, orally disintegrable dosage forms must be individually packaged in a very protective and an expensive blister pack. However, the tablets of the present invention can be placed in conventional openable and recloseable multi-tablet bottles or other similar packaging. That is to say that in accordance with the present invention, it is possible to provide more than a single dose in the lumen of a single, reopenable and recloseable package. Not only are such packages considerably less expensive over the cost of the number of tablets provided, but also far more efficient in terms of processing. In addition, two sided folders and other relatively soft, plaint envelope-type packages may be used in combination with the tablets in accordance with the present invention. It is not possible to use such packages, or even less protective blister packs, with the relatively friable orally disintegrable tablets of the prior art.

In addition, in accordance with the present invention, conventionals tablet feeders can be used to feed the tablets into any type of packaging equipments. The friable tablets of the prior art do not withstand traditional hoppering or storage. They also cannot withstand the forces involved in traditional feeding systems. Such systems normally consist of mechanisms, which take bulk random tablets, capture them, align them, and place them into a package. This provides a tremendous advantages in terms of the processibility of the tablets of the present invention as well as reduction in capital expenditures. Using the present invention, one can produce tablets which can be processed through a conventional tabletting equipment.

It is also surprising that rapidly disintegrating tablets of the present invention can be manufactured with high levels of lubricant(s), and also that the lubricant blend time of 10 to 25 minutes or greater can be used without compromising compressibility, disintegration and dissolution of the tablets.

The fast dissolving dosage form prepared according to present invention is found to be very robust and easy, as it does not require the use of solvents and/ or binders and/ or drying as in the case of dosage forms manufactured by other formulation technologies such as spray drying, freeze drying or wet granulation. Fast disintegrating dosage forms of thermolabile drugs can also be obtained through the present invention. The drugs having poor flow property and low bulk density can also be easily formulated. The present invention also allows formulation of fast disintegrating dosage form of both water-soluble and water insoluble active pharmaceutical ingredients.

Also dosage form manufactured accordingly may provide increased bioavailability as the dosage form may bypass the first-pass metabolism of drugs through pregastric absorption from mouth, pharynx, and esophagus. The dosage form also may have faster absorption, especially for drugs having mouth or upper part of gastro-intestinal tract as an absorption window.

The pharmaceutical dosage form prepared accordingly when comes in contact with physiological secretion(s) of the mouth, results in a very fine dispersion in the oral cavity with better mouth feel and good patient compliance and provides better therapeutic efficacy and may improve patient compliance and convenience.

The pharmaceutical dosage form and composition pertinent to the present invention does not require water for the administration of the said dosage form. This may provide better patient compliance and convenience, particularly for children and geriatric patients.

The active pharmaceutical ingredients may be selected from the class of antacids, antihistaminics, non steroidal anti inflammatory agents, steroidal inflammatory agents, antiepileptic agents, analgesics, antiallergic agents, hypnotic agents, antihypertensive agents, antihyperlipidemic agents, antiarrhythmic agents, cardiotonics, antipsychotic agents, bronchodilators, antibiotics, analgesics, antiparkinsonism agents, bronchodilators, diuretics, antidiabetic agents, central nervous system acting agents, memory enhancing agents, mood elevators, antispasmodics, hormone drugs, 5HT receptor antagonists, coronary vasodilators, calcium antagonists, cardiotonic agents, H_2 receptor antagonist, anticancer agents, antigout agents, antidepressant agents, drugs for rheumatoid arthritis, antifungal agents, antiemetic agents, antidiarrheal agents, drugs for sexual dysfunction, biologicals, decongestants and combinations thereof.

Preferred active ingredients selected in the present invention are from the class of NSAIDs, steroidal antiinflammatory agents such as betamethasone, cardiotonic drugs such as digitoxin, analgesics, antihypertensives, H_2 antagonists, antacids, antipyretics, antibiotics, vitamins, minerals and dietary supplements.

NSAIDs, which are suitable, includes diclofenac sodium/potassium, piroxicam, aspirin, nimesulide, ketoprofen, indomethacin, salicylamide, rofecoxib, celecoxib, etoricoxib, parecoxib and the like; skeletal muscle relaxants such as methocarvatol and such other similar drugs may also be used. Analgesics, which are suitable, includes paracetamol, aspirin, ibuprofen and the likes; Antibiotics, which are suitable, include cephams, penams and carbapenams such as cefalexin, cefotaxam, cefazolin, amoxicillin, pivampicillin, doxycycline, actinomycin and the like; Suitable antihistamines may be selected from

diphenhydramine hydrochloride, promethazine, fexofenadin hydrochloride, and the like; Antiemetics may include promethazine, domperidone, metoclopramide, ondansetron, doxylamine succinate and the like;

Antacids may include aluminum hydroxide, magnesium oxide, magnesium carbonate and the like and H_2 antagonists such as cimetidine, ranitidine, famotidine, nizatidine and the like and novel proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole and the like can be used; Antipsychotic agents may be selected from olanzapine, chlorpromazine, thioridazine and the like; Antiepileptic agents may be selected from sodium valproate, carbamazepine, phenytoin and the like; Antivirals such as acyclovir, zidovudine, lamivudine and the like; Antidepressants may be selected from sertraline, imipramine, amitryptyline and the like; Drugs for erectile dysfunction such as sildenafil; Anxiolytic agents may be selected from diazepam, lorazepam, alprazolam, chlordiazepoxide and the like; Antigout agents such as allopurinol; Antihyperlipidemic agents may include atorvastatin, simvastatin, pravastatin, lovastatin and the like; Antiparkinsonism agents may include levodopa, orphinadine and the like; Diuretics such as sulphamethoxazole, coronary vasodilators such as nitroglycerin; Antihypertensive agents may be selected from propranolol, pindolol, amlodipine, lisinopril, nifedipine, atenolol, verapamil, quinapril, enalapril, diltiazem and the like; Vitamins refer to trace organic substances that are required in the diet. Vitamins may be selected from thiamin, pyridoxine, riboflavin, nicotinic acids, biotin and the like; Also included in the term vitamin are coenzymes which may be includes, thiamin pyrophosphate (TPP), flavin mononucleotide (FMN) and the like. The term vitamin also includes choline, carnitine, and alpha, beta and gamma carotenes; The term mineral refers to inorganic substances, metals, and the like required in the diet. Thus the term minerals may includes, without limitation, calcium, (calcium carbonate), zinc, selenium and the like; The term dietary supplement as used herein means a substance which has an appreciable nutrition effect when administered in small amounts. Dietary supplements include, without limitation, such ingredients as bee pollen, bran, wheat germ and the like.

The dosage form prepared according to the present invention consists of any suitable active pharmaceutical ingredient described above along with a disintegrant and moisture absorber optionally in combination with other suitable pharmaceutical excipients.

In the present invention, active pharmaceutical agent may be used in the range from about 0 % to 80 % by weight of the total weight of the composition of the dosage form, preferably 5% to 60 %, more preferably 10 % to 60 % of the total weight of the composition of the dosage form.

Particle size of the active pharmaceutical agent used in the present invention may be in the range from about 35 μm to 2000 μm, preferably from about 35 μm to 1000 μm, and more preferably from about 50μm to 500 μm. The particle size analysis of the active pharmaceutical used in the present invention has been carried out using Malvern Particle Size Analyzer.

Disintegrant used in the present invention may be selected from starches, such as maize starch, rice starch or super disintegrants like, sodium starch glycolate, cross-linked poly-vinyl pyrrolidone, croscarmellose sodium, modified agar, formaldehyde treated casein, or may be used in any combination thereof as is well known in the art. The disintegrating agent may be present in an amount from about 0.5 to 15 %, preferably from about 1 to 10 %, more preferably from about 2 to 5 % by weight of the total weight of the composition of the dosage form. Preferable disintegrating agent can be selected in the present invention are croscarmellose sodium, sodium starch glycolate, cross-linked poly vinyl pyrolidone or treated agar.

Other necessary excipients which may be used in the present invention includes, diluents, moisture absorber, dry binder, sweetener, flavor, colors and lubricants as are well known in the art.

Diluents used in the present invention may be selected from the group consisting of mannitol, lactose, sorbitol, directly compressible starch, micro crystalline cellulose, dibasic calcium phosphate dihydrate and the like. Preferable diluents of the present invention includes but not limited to mannitol, sorbitol and microcrystalline cellulose and the like. Diluent used in the present invention may vary from about 5 to 90 % by weight of the total weight of the composition of the dosage form.

Moisture absorber useful in the present invention may include microcrystalline cellulose, silica gel and such like. Preferably, microcrystalline cellulose in the range of about 0.5 to 20 % and more preferably, from about 2 to 10 % by weight of the total weight of the composition of the dosage form is used.

Binders, which may be used optionally in the present invention are preferably, dry binders and include pregelatinised starch, cellulosic derivatives, acacia, tragacanth, gelatin and the like. The binders may be present in an amount from about 0.5 to 10% by weight of the total weight of the composition of the dosage form.

Suitable sweeteners useful in the present invention include but not limited to glucose, dextrose, fructose, saccharin and its various salt like sodium saccharin, aspartame, glycyrrhizin and the likes as well known in the art.

Optionally, flavors well known in the art may be added, for example, citrates like lemon, grasp, peppermint, orange and other flavors like banana, pineapple, raspberry, cherry, strawberry, mango, peach, pear and the likes to provide suitable flavor as may be desirable.

Colors used in the present invention may be selected from food drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C) or external drug and cosmetic colors (Ext. D&C) as are desirable. These colors can be lakes, dyes or certain natural or derived colors.

Lubricants useful in the present invention may be selected from magnesium stearate, silicon derivatives like anhydrous silicon dioxide (Aerosil), talc, glyceryl behanate, polyethylene glycols, stearic acid and the likes. The lubricants may be present from about 0.2 to 5% by weight of the total weight of the composition of the dosage form.

Process for preparation of the tablets

Present invention relates to the process for the preparation of superior fast dissolving or fast disintegrating dosage forms by means of dry granulation technique. The present invention involves three steps. In the first step, the high-density flakes or slugs of either the mixture of active pharmaceutical ingredient (API) and pharmaceutically acceptable excipients or API alone or excipients alone are obtained by means of roller compaction or slugging. In second step, the obtained flakes or slugs may be screened using suitable equipment such as oscillating granulator, to obtain the granules of desired size. In third step, these granules are compressed into tablets or processed suitably to obtain wafers or may be packed as such in suitable packaging.

Active pharmaceuticals used in the present invention were passed through a sieve with aperture size ranging from about 0.037mm to 2mm (Sieve no. # 10 to 400 ASTM standards sieve) and in a preferred embodiment of the present invention, the active pharmaceutical is passed thorough a sieve (ASTM # 200).

All other excipients used in the present invention may be passed using a suitable mill, through a sieve ranging from about ASTM sieve #10 to # 200, preferably 20 to 100 ASTM standard sieve. The drug is mixed with all excipients in dry state. Mixing time in the present invention may vary from about 5 min to 20 minutes depending on the drug.

The powder mixture may be subjected to dry granulation technique using roller compactor or slugging. Usually during dry granulation technique, 50% of the lubricants are added before compacting the blend to get proper flow of powder mixture. This can be avoided by using roller compactor having horizontal and vertical feed auger.

Roller compaction may be carried out by passing the drug and/or drug along with the other excipient between the two rollers of the roller compactor. The rollers may be

maintained at a necessary gap ranging from 0.5mm to 5 mm, which may be varied by means of hydraulic pressure or by any other suitable means known to those in the art. The drug and/or drug along with the other excipients may be added to the hopper and the blend may be made to pass between the rollers with horizontal and vertical feeder. The speed of the horizontal and vertical feeder may be at 5 to 20 rpm. The rollers may be maintained at a suitable pressure ranging from about 20-250 Kg/cm^2, and preferably in the range of 50-200 Kg/cm^2 with the maximum applicable pressure of 250 Kg/cm^2.

Obtained flakes having different thickness may be in the range of 0.2 mm to 2mm. The Compacted flakes may be milled and sieved to achieve granules of desired size. The compacted flakes in the present invention may be sieved through a sieve ranging from about 10 to 40 # (ASTM), precisely through 10-30 # (ASTM). The property of the granules may vary with the compacting force applied during the dry granulation technique.

The granules obtained in the present invention may be fragile/brittle or hard depending on the applied pressure. The property of the granules may be varied by certain parameters such as speed of the roller, distance between the roller i.e., applied pressure and feed rate. Speed of the roller in the present invention may be in the range of 1 to 50 rpm. Feed rate may be controlled by the speed of horizontal and vertical feeder (auger). The speed of both the feeders in the present invention may vary from 2 to 50 rpm.

In slugging, slugs of the active pharmaceutical ingredient and/or required pharmaceutical excipients or of the excipients alone are obtained using a rotary tablet machine with applied pressure in the range of 2 ton to 8 tons. Here, for the flow of the powder mixture from hopper, forced powder feeder is required or the powder mixture is lubricated with lubricants. Lubricants, as said in the prior art, may be used in the range of 0.2 % to 5% of the total weight of the powder mixture. Slugs prepared may then be sieved using suitable equipments known to those in the art to obtain desired size granules.

The granules obtained in the present invention may be lubricated with one or a mixture of lubricants, which may be present in the range from 0.2 to 5 %. The lubricated granules may be compressed into tablets using conventional rotary tablet machine and checked for the pharmacotechnical characteristics including surface property, disintegration time, dispersion pattern, mouth feel, friability, hardness and finally mouth dispersion time.

The following non-limiting examples describe the innovative means of process to carry out the invention to obtain a superiorly fast-disintegrating / mouth disintegrating / rapidly disintegrating tablets by means of dry granulation.

The invention is more precisely described by the following non-limiting examples:

EXAMPLE 1:

Composition of the granulate:

API/Excipients	Weight %
Rofecoxib	16.63
Mannitol	77.12
AC-Di-Sol	4.0
Silica Gel	2.0
Sodium Saccharine	0.10
Color yellow iron oxide	0.15
Flavor	2.0

To prepare these granules, drug is milled and passed through sieve # 150 (ASTM). All other excipients are passed through a sieve 100(ASTM). Mixing is carried out for about 10 minutes. This mixture is passed through the feeder of the roller compactor (KMRC-2, Kevin Engineering, Ahmedabad). Horizontal shaft is operated at a speed of 10-20 rpm and vertical shaft is operated at a speed of 15-25 rpm. Pressure between two rollers is adjusted, such that maximum compacted mass comes out, and is in between 50-250 kg/cm^2. Speed of the rollers are in between 5-40 rpm. The cycle of compaction is repeated until required quality flakes are formed. These compacted flakes are further subjected to dry granulation.

EXAMPLE 2:

Preparation of tablets

Preparation of tablets	
Prepared granulate	98 %
Aerosil	1.0 %
Magnesium stearate	1.0 %

To these compacted granules lubricants, previously passed through sieve a 100 ASTM, are added and mixed for 5 minutes in cube blender. These lubricated granules are compressed into tablets using 12/32" punches in a rotary tablet machine. Prepared tablets are having hardness in the range of 2 to15 Kp. These tablets showed disintegration time of about 0.25-3 minutes in USP disintegrating apparatus with a friability in the ranging from about 0.5-0.6 %. Assay of the tablets is within the specified range (± 5 %).

EXAMPLE 3

Granulates are prepared using the same adjutants with the following changes as explained in the example-1.

Ac-Di-Sol	6 %
Silica gel	4 %
Mannitol	as required

Mixing time is increased up to 20 minutes.

EXAMPLE 4

Tablets are prepared using the same procedure as explained in the example-2.

These tablets showed disintegration time in the range from about 0.2-1 minute with a friability ranging from about 0.6 to 0.8 %. Tablets assay showed ±3% variation.

EXAMPLE 5:

Composition of the granulate:

API/Excipients	Weight %
Rofecoxib	16.63
Mannitol	77.12
Cross PVP	4.0
Microcrystalline cellulose	2.0
Sodium Saccharine	0.10
Color yellow iron oxide	0.15
Flavor	2.0

The granulates are prepared with a method as explained in the example-1.

EXAMPLE 6:

Preparation of tablets

Prepared granulate	98 %
Aerosil	1.0 %
Magnesium stearate	1.0 %

The tablets are prepared by a method as explained in the example-2

These tablets showed disintegration time between 0.5-1 minutes with a friability in the range from about 0.2-0.3 %.

EXAMPLE 7: Composition of the granulate:

API/Excipients	Weight %
Rofecoxib	16.63
Mannitol	77.12
Sodium starch glycolate	4.0
Silica Gel	2.0
Sodium Saccharine	0.10
Color yellow iron oxide	0.15
Flavor	2.0

The granulates are prepared with a method as explained in the example-1. The tablets are prepared by a method as explained in the example-2

Tablets prepared from this batch showed disintegration time ranging from about of 0.25-3 minutes with a friability in the range from about 0.5-0.7 %.

EXAMPLE 8: Composition of the granulate:

API/Excipients	Weight %
Nimesulide	33.26
Mannitol	58.49
Ac-Di-Sol	4.0
Microcrystalline cellulose	2.0
Sodium Saccharine	0.10
Color Red Iron Oxide	0.15
Flavor	2.0

The granulates are prepared with a method as explained in the example-1. The tablets are prepared by a method as explained in the example-2

Tablets prepared showed disintegration time in the range from about 0.5 -1 minutes.

We claim:

1. A process of preparing mouth dissolving solid oral pharmaceutical dosage forms by dry granulation technique which comprises blending the active pharmaceutical agent with a moisture absorber in the range of 0.5 to 20 % by weight of total composition and a disintegrating agent in the range of 0.5 to 15 % of the total composition and compacting the blend to obtain granules.
2. The process according to claim 1 wherein the active pharmaceutical agent is blended with disintegrant, moisture absorber and optionally with other pharmaceutical excipients such as dry binders, diluents, lubricants, sweetners, active stabilizers, taste neutralizing agents, colouring agents and flavoring agents.
3. The process according to claims 1 & 2, wherein the disintegrants are selected from the group consisting of starch and starch derivatives such as potato starch; cellulose like microcrystalline cellulose, hydroxy propyl methyl cellulose; effervescent agents such as citric or tartaric acid with sodium bicarbonate; sodium alginate, crospovidone, croscarmellose sodium and sodium starch glycolate.
4. The process as claimed in claim 1 & 2 wherein the disintegrating agent is present in an amount from about 0.5 to 15 % by weight of the total composition of the dosage form.
5. The process as claimed in claim 1 wherein the moisture absorber is selected from the group consisting of silica derivatives such as silica gel and celluloses such as microcrystalline cellulose.
6. The process as claimed in any preceding claims wherein the moisture absorber is present in an amount from about 0.5 to 20 % by weight of the total composition of the dosage form.
7. The process as claimed in claims 1 & 2 wherein the dry binders are selected from the group consisting of acacia, tragacanth, microcrystalline cellulose, pregelatinised starch, hydroxypropyl cellulose, and hydroxypropyl methylcellulose
8. The process as claimed in claim 7 wherein the dry binder is present in an amount from 0.5 to 10% by weight of the total weight of the composition of the dosage form.
9. The process as claimed in claims 1 & 2 wherein the diluents are selected from the group consisting of lactose, mannitol, glucose, fructose, sorbitol, xylitol, calcium phosphate, calcium sulphate and maltodextrin.
10. The process as claimed in claim 9 wherein the diluent is present in an amount from 5 to 90 % by weight of the total weight of the composition of the dosage form.

11. The process as claimed in claims 1 & 2 wherein the lubricants are selected from the group consisting of talc, stearic acid, magnesium stearate, aerosil and stearyl fumarate.
12. The process as claimed in claim 11 wherein the lubricant is present in an amount from 0.2 to 5% by weight of the total weight of the composition of the dosage form.
13. The process according to claim 1 wherein the compaction is done by roller compaction or by slugging.
14. The process according to any preceding claims wherein the prepared granules are either compressed into tablets, wafers or filled as such into sachets.
15. The process according to any preceding claims wherein the said dosage forms disintegrates in the mouth within 5 – 90 seconds.
16. The process according to any preceding claims wherein the active agent dissolves rapidly and imparts quick therapeutic activity.
17. The process according to any preceding claims wherein the active ingredients are selected from the group consisting of antacids, antihistaminics, non steroidal anti inflammatory agents, steroidal inflammatory agents, antiepileptic agents, analgesics, antiallergic agents, hypnotic agents, antihypertensive agents, antihyperlipidemic agents, antiarrhythmic agents, cardiotonics, antipsychotic agents, bronchodilators, antibiotics, analgesics, antiparkinsonism agents, bronchodilators, diuretics, antidiabetic agents, central nervous system acting agents, memory enhancing agents, mood elevators, antispasmodics, hormone drugs, 5HT receptor antagonists, coronary vasodilators, calcium antagonists, cardiotonic agents, H_2 receptor antagonist, anticancer agents, antigout agents, antidepressant agents, drugs for rheumatoid arthritis, antifungal agents, antiemetic agents, antidiarrheal agents, drugs for sexual dysfunction.
18. The process according to any preceding claims wherein the pharmaceutically active agent is selected from the group consisting of rofecoxib, celecoxib, parecoxib, valdecoxib, etoricoxib, diclofenac sodium, nimesulide, piroxicam, omeprazole, ranitidine, famotidine, citrizine, leocitrizine, betamethasone, olanzapine, alprazolam, sodium valproate, levodopa, aspirin, ondansetron, sulphamethoxazole, nitroglycerine, pindolol, digitoxin, diltiazem hydrochloride, fexofenadine hydrochloride, doxycycline, actinomycin, allopurinol, quinapril, atorvastatin, simvastatin, pravastatin, lovastatin, lamivudine, sildenafil, sertraline and enalapril.
19. A fast disintegrating oral dosage form prepared according to the present invention consisting of 1 % to 80 % of the active pharmaceutical ingredient by weight of the total weight of the composition of the dosage form as described above, 0.5 to 15 % of

disintegrating agent, 0.5 to 20% of moisture absorber, the rest, if any, consist optionally of binders, diluents, lubricants, sweeteners, colouring and flavouring agents.

20. The process according to any preceding claims is more suitable for moisture sensitive pharmaceutical agents.

21. The process according to any preceding claims, is highly suitable for low bulk density active pharmaceuticals and also for actives having low compressibility.